REMARKS

Reconsideration of the allowability of the present application is requested respectfully.

Status of the Claims

All of the pending claims, that is, claims 1 to 11 and 21 to 31 have been acted upon by the Examiner. No claims have been allowed. Claims 2 to 4, 7, 10, and 30 have been amended. Claims 1 and 29 have been canceled. Claims 32 to 34 have been added. Claims 2 to 11, 21 to 28, and 30 to 34 are presented for examination.

Claims 2 to 4, 7, 10, and 30 have been amended to depend from Claim 1. Support for these amendments may be found throughout the application, particularly from page 11, line 20, to page 12, line 2, and on page 18, lines 1 to 20 of the application.

Support for new claims 32 to 34 may be found from page 11, line 20, to page 12, line 2.

ARGUMENTS

Summary of the Rejections

The 35 U.S.C. §112, second paragraph, Rejections

The Examiner has rejected Claims 1 to 11, 29 and 30 under 35 U.S.C. §112, second paragraph, for failing to particularly point out and distinctly claim the subject matter of the invention. Independent claims 1 and 29 have been canceled without prejudice. Claims 2 to 11 and 30 have been amended to depend, directly or indirectly, from Claim 31. As Claim 31 comprises a means of cryopreservation, (i.e., means for providing, washing, detaching, suspending, and storing transfected BMSCs) applicants respectfully request withdrawal of the Examiner's rejections under 35 U.S.C. §112, second paragraph.

The 35 U.S.C. §103(a) Rejections

The Examiner has presented a variety of §103 rejections, each of which is discussed in turn below. Applicants submit that there are essentially two main flaws in the Examiner's reasoning regarding the present obviousness rejections: 1) the Examiner asserts that any cryopreservation medium can be used on any cell type, and 2) the Examiner asserts that any culture medium can be used as a component of a cryopreservation solution for any cell type. Both of these assertions are incorrect and do not provide a proper basis for the present §103 rejections.

In addition to Zaheer et al. publication, cited in applicants' last reply, the Brinster and Rowley publications (cited by Examiner in the present action) also state that different cryopreservation techniques will have different effects on different cell types. Although the Examiner has asserted the obviousness of cryopreserving transfected BMSCs, the Examiner has failed to produce a single reference that discloses cryopreservation of BMSCs. The Examiner has only cited references that

disclose cryopreservation of mixed cell populations (e.g., bone marrow) or non-BMSC cell types (e.g., lymphocytes).

Furthermore, the Examiner's assertion that the cryopreservation medium of the presently claimed invention is a "standard" solution is not supported by the cited references. Not a single reference cited discloses the cryopreservation of any cell type, let alone transfected BMSCs, with a cryopreservation medium comprising 10% dimethyl sulfoxide (DMSO), about 1-50% fetal bovine serum (FBS), and about 89-40% Dulbecco's modified Eagles' medium (DMEM), as presently claimed in Claim 31.

In addition, the Examiner's assertions that DMEM and McCoy's 5A medium are equivalent to each other is incorrect. If the specific passages of the references cited are interpreted as the Examiner has interpreted them, the result would be that all culturing media is equivalent. This is clearly not the case. Furthermore, Emerson et al., cited by the Examiner, clearly indicates that DMEM and McCoy's 5A medium comprise different components at different concentrations.

The 35 U.S.C. §103(a) Rejections of Claims 1 to 5, 7 to 9, 21, 22, 24 to 26, and 29 to 31

The Examiner has rejected Claims 1 to 5, 7 to 9, 21, 22, 24 to 26, and 29 to 31 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,399,346 ("Anderson et al.") taken with European Patent Application No. 0381490 ("Greenberger et al."), Boswell et al. Exp. Hematol. 11:315-323 (1983), U.S. Patent No. 6,326,198 ("Emerson et al."), Yamada et al. Nagoya J. Med. Sci. 44:117-131 (1982), U.S. Patent No. 5,817,453 ("Brinster"), Rowley

Hematotherapy 1:233-250 (1982), and as evidenced by Hacker et al. Proc. Am. Assoc. Cancer Res. 16:66 (1975).

The discussion below will illustrate that

(A) Anderson et al. does not provide a motivation to combine references;

(B) The teaching of Greenberger et al. is incompatible with Anderson et al;

(C) Boswell et al. does not teach cryopreservation of BMSCs but instead teaches cryopreservation of a mixed population of cells using a cryopreservation medium that differs from the presently claimed cryopreservation medium;

(D) Emerson et al. does not teach cryopreservation of BMSCs but instead teaches cryopreservation of mixed populations of cells and does not disclose that DMEM and McCoy's 5A medium are equally effective in culturing BMSCs;

(E) Yamada et al. does not teach cryopreservation of BMSCs and discloses a cryopreservation medium that differs from the presently claimed cryopreservation medium;

(F) Brinster does not teach cryopreservation of BMSCs but instead discloses a cryopreservation medium that differs from the presently claimed cryopreservation medium and does not disclose that DMEM and McCoy's 5A medium are equally effective in culturing BMSCs;

(G) Rowley does not teach cryopreservation of BMSCs and discloses a cryopreservation medium that differs from the presently claimed cryopreservation medium; and

(H) Hacker et al. does not disclose any elements of the presently claimed invention.

Anderson et al. does not provide a motivation to combine references

Anderson et al. discloses transfection of tumor-infiltrating lymphocytes (TILs) and the cryopreservation of transfected TILs. The means for cryopreserving the transfected TILs is not disclosed. The examiner has asserted that Anderson et al. provides motivation for crypopreservation of any and all genetically modified cells.

Applicants submit that whether Anderson et al. provides motivation to cryopreserve transfected cells is irrelevant to a determination of obviousness. Clearly applicants have recognized a need to cryopreserve transfected BMSCs and have addressed that need. For obviousness to be established, it is necessary to provide a *motivation to combine references* to produce the claimed invention, **not merely** a motivation to make the claimed invention. MPEP §2143.01 recites:

> Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also >*In re Lee,* 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references);< *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

To recognize a motivation to make an invention is simply another way of recognizing that the invention has utility. To recognize *a motivation to combine references* to make an invention is part of a determination of nonobviousness. The Examiner has attempted to provide reasons why one of skill in the art would be motivated to make the claimed invention. But such motivation is not what is required by MPEP §2143, namely, a motivation to combine reference teachings.

As discussed below, the Examiner has provided no motivation to combine the cited references and as such has not established a *prima facie* case of obviousness. Guidance on the requirements for combining publications in an obviousness rejection is provided by the MPEP §2143. "The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record." *In re Sang-Su Lee*, 277 F. 3d 1338, 1343, (C.A.Fed. 2002) emphasis added; see MPEP (8th Ed. Rev. 1 Feb. 2003) §2143.01. Also, "the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination. In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious." *In re Rouffet,* 149 F.3d 1350, 1359, (Fed.Cir.1998).

The teaching of Greenberger et al. is incompatible with Anderson et al.

Greenberger et al. discloses using bone marrow stromal cells (BMSCs) for gene therapy, but does not teach cryopreservation of BMSCs. Although cryopreservation is not discussed in Greenberger et al., the Examiner has asserted that cryopreservation is an integrated part of any cell culture procedure of continued cell preservation.

None of the cited publications contains any suggestion or motivation to modify or combine the publication teachings so as to render the claimed invention obvious. One of skill in the art would not combine a publication on TILs (Anderson et al.) with a publication on BMSCs (Greenberger et al.).

What is missing from the Examiner's prima facie case of obviousness is evidence why one of skill in the art would be motivated to particularly choose Anderson et al. and combine it with Greenberger et al. What is the motivation for a skilled artisan, knowing that TILs and BMSCs respond differently to cryopreservation, to choose the teachings of a TIL reference in order to successfully cryopreserve BMSCs? Conclusory statements regarding such motivation, such as "because the claimed invention is beneficial", do not satisfy the requirements of the USPTO for a §103 rejection.

Applicants have provided substantive reasons (reiterated below) for why one would not combine a TIL publication with a BMSC publication. In contrast, the Examiner has not provided a proper, rule-based basis to combine the publications. As explained above and in the cited cases, the mere recognition that cryopreserved transfected BMSCs are desirable does not satisfy the requirement that the Examiner provide objective evidence as to why a skilled artisan would combine a TIL publication with a BMSC publication.

Applicants have explained that TILs and BMSCs are fundamentally different types of cells that react differently to cryopreservation. To support this position, Applicants submitted with the Reply dated August 23, 2002: a publication by Zaheer et al. ("Differential sensitivity to cryopreservation of clonogenic progenitor cells and stromal precursors from leukemic and normal bone marrow," Stem Cells 12:180-186 (1994)).

Zaheer et al. was published in 1994 and thus is an example of the state of the cryopreservation art at the time of the earliest priority date for the present

application (December 29, 1995). The Mediatech document was copyrighted in 2001 and made available on the internet at an unknown date.

To help clarify Applicants' position the experimental findings disclosed in Zaheer et al. are summarized below. However, before discussing Zaheer et al. applicants believe it would be helpful to provide some background information on bone marrow cells and stem cells.

Bone marrow comprises many different cell types. Among these cell types are stem cells. Stem cells can differentiate into many other cell types. Before stem cells become fully differentiated, they first go through an intermediate or progenitor phase wherein the cells are committed to a specific lineage, but are technically not fully differentiated. These progenitors later become fully differentiated cells (e.g., a lymphocyte or TIL). One common characteristic shared by stem cells, progenitor cells, and the fully differentiated cells is that they are all nonadherent cell types.

Stromal cells are also found in bone marrow. In contrast to nonadherent cell types, stromal cells grown *in vitro* form a layer that adheres to a tissue culture dish. Thus, they are referred to as "adherent" cells. It is undisputed that one of skill in the art would recognize that a TIL is similar to a non-adherent progenitor cell and that, in contrast, a BMSC is an adherent stromal cell.

Zaheer et al. cryopreserved bone marrow cells (a mixture of stromal cells and progenitor cells) and then thawed the cells. These thawed cells were compared to bone marrow cells that had never been frozen. In this regard, the cryopreserved progenitor cells acted very similarly to non-cryopreserved progenitor cells. The

cryopreserved progenitor cells were able to proliferate and differentiate just as well as non-cryopreserved progenitor cells.

A very different result was seen for the stromal cells. The stromal cells recovered after cryopreservation could not form a stromal layer (see paragraph bridging pages 182 and 183 of Zaheer et al.). Also, and more critically, cryopreserved stromal cells could not support proliferation and differentiation of progenitor cells (page 182, column 2, lines 13 to 20) as measured by using long-term bone marrow culture (LTBMC). LTBMC is an assay comprising growing progenitor cells in the presence of a stromal layer and then determining if proliferation and/or differentiation of progenitors occurs. Thus, when cryopreserved progenitor cells were grown on a non-cryopreserved, pre-formed stromal layer, proliferation and differentiation did occur (page 185, column 2, lines 11 to 15). In contrast, when cryopreserved progenitor cells were grown on a cryopreserved stromal layer, proliferation and differentiation did not occur (page 182, column 2, lines 13 to 20).

The conclusion of Zaheer et al. is that cryopreservation did not affect the progenitor cells but did have an effect on the stromal cells. Thus, adherent stromal (including BMSCs) cells react differently to cryopreservation than do nonadherent progenitor cells (similar to TILs).

Applicants submitted the Zaheer et al. publication to demonstrate the thinking in the art about the time of the present invention and to further demonstrate why the skilled artisan would not combine Anderson et al. with either Greenberger et al. or Boswell et al. Clearly, cryopreservation has affected the ability of the stromal cells to grow and express genes necessary to support progenitor growth and

differentiation. In contrast, cryopreservation does not affect the ability of progenitor cells (which are precursors to TILs) to grow and differentiate.

Applicants submit that, in view of Zaheer et al., one of skill in the art would not look to a method of cryopreserving TILs in order to cryopreserve transfected BMSCs. Thus, there is no basis to combine the cited publications as the Examiner has done.

Boswell et al. does not teach cryopreservation of BMSCs; Boswell et al. teaches cryopreservation of a mixed population of cells

The Examiner has asserted that Boswell et al. discloses details of cryopreservation of both hematopoietic stem cells and BMSCs. This is incorrect. Boswell et al. discloses cryopreservation of total bone marrow, not hematopoietic stem cells and BMSCs separately. In particular, Boswell et al. does not disclose cryopreservation of BMSCs alone. One of skill in the art would recognize that freezing cells as part of a larger population of cells is different than freezing individual cell types. To characterize Boswell et al. as teaching details of cryopreservation for both hematopoietic stem cells and BMSCs is misleading. Using the Examiner's reasoning, a reference that discloses cryopreservation of a human being also teaches suitable cryopreservation for both hematopoietic stem cells and BMSCs. If the Examiner wishes to maintain this rejection, it is respectfully requested that the Examiner provide evidence why one of ordinary skill in the art would combine a reference that discloses cryopreservation of a mixed population of untransfected cells with references that disclose cryopreservation of only single cell types which have been transfected.

Boswell et al. discloses a cryopreservation medium that differs from the presently claimed cryopreservation medium

The cryopreservation medium of Boswell et al. differs from the cryopreservation medium of the present claims. Claim 31 is directed to a cryopreservation medium comprising 10% dimethyl sulfoxide (DMSO), about 1-50% fetal bovine serum (FBS), and about 89-40% Dulbecco's modified Eagles' medium (DMEM). The cryopreservation medium of Boswell et al. comprises 10% DMSO, 20% FBS, and 70% McCoy's Medium.

Emerson et al. does not teach cryopreservation of BMSCs; Emerson et al. teaches cryopreservation of mixed populations of cells

Similar to Boswell et al., the Examiner has asserted that Emerson et al. teaches the proper culture medium of both hematopoietic stem cells and BMSCs. This is incorrect. Emerson et al. discloses culturing of human peripheral blood mono-nuclear cells, human bone marrow cells, human fetal liver cells, and/or human cord blood cells (see column 7, lines 15 to 20 of Emerson et al.). In fact, Emerson et al. discloses that BMSCs need not even be present in the cultures. Column 8, lines 11 to 12 recites, "Bone marrow stromal cells may or may not be present in the cultures of the invention." Thus, Emerson et al. is directed to mixed cell cultures, which may or may not include BMSCs. Emerson et al. does not disclose culturing of transfected BMSCs and furthermore does not disclose cryopreservation of transfected BMSCs.

Emerson et al. does not disclose that DMEM abd McCoy's 5A medium are equally effective in culturing BMSCs

The Examiner has also made the assertion, based on Emerson et al., that McCoy's 5A and DMEM media are equally effective in culturing BMSCs.

Regarding culturing of BMSCs, as noted above, Emerson et al. does not disclose culturing of BMSCs. Also, Emerson et al. does not disclose that McCoy's 5A and DMEM are equal. The Examiner has attempted to support this contention by referencing two pages of charts and a single sentence of Emerson et al. However, the charts of columns 9, 10, 19, and 20 indicate that the components of McCoy's 5A and DMEM media are *different*, not equal. One need to look no further than the first two lines to see that McCoy's has about half the $CaCl_2$ of DMEM, and that DMEM contains $Fe(NO_3)_2$ $9H_2O$ while McCoy's 5A does not. They also differ with regard to most of their other components as well. Considering their different compositions, there is no basis to suggest they are "equally effective."

The Examiner has also relied on column 8, lines 37 to 42, of Emerson et al. which recites:

> Illustratively, the medium used in accordance with the invention may comprise three basic components. The first component is a media component comprised of IMDM, MEM, DMEM, RPMI 1640, Alpha medium, or McCoy's Medium, or an equivalent known culture medium component.

Clearly, the Examiner has interpreted the passage above to indicate that each of these media types, IMDM, MEM, DMEM, RPMI 1640, Alpha medium, or McCoy's Medium, is equivalent or interchangeable with each other. This is incorrect. One of ordinary skill in the art would recognize that different cell types react differently to different media. The phrase "...or an equivalent known culture medium component" refers to an equivalent of any individual media type. It does not indicate that all of the aforementioned media are all equivalent. Emerson et al. discloses that each of these media comprise different concentrations of chemical components. They are clearly not chemically equivalent to each other. Accordingly, the Examiner's assertion, based on Emerson et al., that McCoy's 5A

and DMEM media are equally effective in culturing BMSCs is undermined by 1) Emerson et al. does not disclose culturing of BMSCs, and 2) Emerson et al. discloses that McCoy's 5A and DMEM media comprise different chemical components.

Yamada et al. does not teach cryopreservation of BMSCs; Yamada et al. discloses a cryopreservation medium that differs from the presently claimed cryopreservation medium

Yamada et al. teaches the general state of the art of cryopreservation of peripheral blood lymphoid cells. Yamada et al. does not disclose cryopreservation of any type of transfected cell nor does it disclose cryopreservation of BMSCs. The means of cryopreservation disclosed by Yamada et al. includes a cryopreservation medium comprising 20% DMSO, 20% FBS, 60% RPMI 1640 Medium and a decrease of temperature to less than -80°C . Claim 31 is directed to a cryopreservation medium comprising 10% DMSO, about 1-50% FBS, and about 89-40% DMEM. As disclosed in Emerson et al. (compare columns 9 to 12 with columns 17 and 18 of Emerson et al.), DMEM and RPMI 1640 are vastly different types of media. Similar to McCoy's 5A medium, one need to look no further than the first two lines of these columns to see that RPMI 1640 has about half the $CaCl_2$ of DMEM, and that DMEM contains $Fe(NO_3)_2$ $9H_2O$ while RPMI 1640 does not. They also differ with regard to most of their other components as well.

Brinster does not teach cryopreservation of BMSCs; Brinster discloses a cryopreservation medium that differs from the presently claimed cryopreservation medium

The Examiner has also cited Brinster, which has a filing date of May 31, 1996. Applicants note that as the filing date of Brinster is after the earliest priority

date of the present application, December 29, 1995, Brinster may have been cited improperly. Brinster discloses cryopreservation of spermatogonia cells transfected with LacZ. The Examiner has asserted that a cryopreservation medium comprising 10% FBS, 80% DMEM, 10% DMSO (a ratio of 1:8:1) was used. This is incorrect. Column 25, lines 35 to 37, recites, "Freezing medium (FBS, DMEM-C, DMSO in a ratio of 1:3:1) was added slowly by drops to equal the original cell volume." Accordingly, a "1:3:1 ratio" would indicate that the cryopreservation medium comprises 20% FBS, 60% DMEM-C, and 20% DMSO. Such a cryopreservation medium is not utilized by the present claims. Accordingly, the Examiner's assertion that Brinster disclosed a "standard" cryopreservation technique is irrelevant as the present claims are directed to the use of a cryopreservation medium that differs from Brinster.

Furthermore, Brinster is directed to techniques of cryopreserving spermatogonia, which are haploid, flagellar, non-adherent cells. The present claims are directed to BMSCs, which are diploid, non-flagellar, adherent cells. These two cell types are vastly different. If the Examiner wishes to maintain this rejection, it is respectfully requested that the Examiner provide evidence why one of ordinary skill in the art would combine a reference that discloses cryopreservation of a haploid, flagellar, non-adherent cell with references that disclose cryopreservation of mixed cell populations and single cell types which are diploid, non-flagellar, adherent cells. Column 21, lines 36 to 41, of Brinster recites (emphasis added):

> Spermatozoa from a number of species can be cryopreserved and then subsequently used to fertilize eggs. However, this technique has several limitations. First, <u>the freezing protocol varies for each species and must be determined empirically, and for some species appropriate methods have not yet been identified</u>.

Accordingly, Brinster teaches that even the same cell types from different species react differently to cryopreservation. This in direct contrast to the Examiner's attempts to merely substitute one cell type (or mixed cells) for another and exchange one cryopreservation medium for another. Brinster underscores the difficulty of cryopreservation and thus increases the importance of the applicants' invention.

Brinster does not disclose that DMEM and McCoy's 5A medium are equally effective in culturing BMSCs

The Examiner has also asserted that Brinster teaches that DMEM and McCoy's 5A medium are "equally effective" for cryopreservation. As support for this assertion, the Examiner has cited column 7, lines 18 to 20. of Brinster. However, this assertion ignores the sentences preceding this section. Column 7, lines 13 to 21, of Brinster recites (emphasis added):

> The medium used to culture the primitive cells may comprise three basic components. The first component is a general media component, the second is a serum component and the third is a special factor component. Standard known media components such as, for example, IMDM, MEM, DMEM, RPMI 1640, Alpha Medium of [sic] McCoy's Medium can be used and can contain combinations of serum albumin, cholesterol and/or lecithin, selenium and inorganic salts.

Clearly, the above passage refers to medium to culture cells, not cryopreserve them. Furthermore, the passage refers to DMEM and McCoy's Medium as known media components, not equivalent media components. Considering the passage refers to the culture of almost any cell type, it's not surprising that almost all media types are represented. As noted above, one of ordinary skill in the art would recognize that different cell types react differently to different media. To imply that IMDM,

MEM, DMEM, RPMI 1640, Alpha Medium and McCoy's Medium can all be used interchangeably is incorrect.

Rowley does not teach cryopreservation of BMSCs

Rowley teaches techniques for cryopreservation of peripheral blood-derived hematopoietic stem cells (PBSCs and HSCs, respectively), a mixed cell population. Rowley does not disclose cryopreservation of BMSCs. However, Rowley does underscore that challenges one encounters when attempting to cryopreserve cells. On page 237, second paragraph, first sentence, Rowley states, "One of the most important concepts of clinical HSC cryopreservation that must be realized is the heterogeneity of marrow and PBSC populations." Thus, as noted above, cryopreserving BMSCs and total bone marrow are vastly different undertakings. The skilled artisan would not expect to be able to interchange cryopreservation techniques for different cell types.

Rowley discloses a cryopreservation medium that differs from the presently claimed cryopreservation medium

Rowley also does not disclose the cryopreservation medium of Claim 31. Indeed, the term "DMEM" does not appear anywhere in Rowley. Table 2 (page 236) of Rowley provides a list of eleven published cryopreservation techniques. Not a single one of the published techniques utilizes DMEM.

Hacker et al. does not disclose any elements of the presently claimed invention

Hacker et al. discloses the effects of cryopreservation on the drug-resistance of leukemic cells. In contrast to the cells used in presently claimed invention, the cells of Hacker et al. had not been transfected. Rather, these cells have an inherent level of drug-resistance. Accordingly, Hacker et al. discloses the effects of

cryopreservation on endogenous DNA, not DNA from an exogenous source. Furthermore, no means of cryopreservation is provided. As Hacker et al. does not disclose BMSCs, transfected cells, or any means of cryopreservation, this reference is does not overcome any of the deficiencies in the §103 rejection discussed above.

In view of the above arguments, applicants respectfully request withdrawal of the rejection of Claims 1 to 5, 7 to 9, 21, 22, 24 to 26, and 29 to 31 under 35 U.S.C. §103(a).

The 35 U.S.C. §103(a) Rejections of Claims 6 and 23

The Examiner has rejected Claims 6 and 23 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,399,346 ("Anderson et al.") taken with European Patent Application No. 0381490 ("Greenberger et al."), Boswell et al. Exp. Hematol. 11:315-323 (1983), U.S. Patent No. 6,326,198 ("Emerson et al."), Yamada et al. Nagoya J. Med. Sci. 44:117-131 (1982), U.S. Patent No. 5,817,453 ("Brinster"), Rowley Hematotherapy 1:233-250 (1982), and further in view of Lozier et al. (*Hum. Gene Ther.*).

Applicants respectfully traverse the rejection.

Lozier et al. has been applied for the teaching of a canine model. The teaching of a canine model provides no basis to overcome the deficiencies of Anderson et al., Greenberger et al., Boswell et al., Emerson et al., Yamada et al., Brinster, and Rowley as noted above. Since Lozier et al. does not provide any information that overcomes the deficiencies in the other cited publications, applicants request respectfully withdrawal of the obviousness rejection of Claims 6 and 23 which additionally relies on Lozier et al.

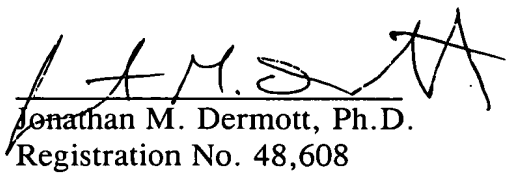
The 35 U.S.C. §103(a) Rejections of Claims 10, 11, 27, and 18

The Examiner has rejected Claims 10, 11, 27, and 18 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,399,346 ("Anderson et al.") taken with European Patent Application No. 0381490 ("Greenberger et al."), Boswell et al. Exp. Hematol. 11:315-323 (1983), U.S. Patent No. 6,326,198 ("Emerson et al."), Yamada et al. Nagoya J. Med. Sci. 44:117-131 (1982), U.S. Patent No. 5,817,453 ("Brinster"), Rowley Hematotherapy 1:233-250 (1982), and further in view of U.S. Patent No. 6,020,188 ("Newman et al.").

Applicants respectfully traverse the rejection.

Newman et al. has been applied for the teaching that the "Cellular adhesion molecules" ("CAMS") include intracellular adhesion molecule-1 (ICAM-1) and neuronal cell adhesion molecule (N-CAM). This teaching provides no basis to overcome the deficiencies of Anderson et al., Greenberger et al., Boswell et al., Emerson et al., Yamada et al., Brinster, and Rowley as noted above. Since Newman et al. does not provide any information that overcomes the deficiencies in the other cited publications, applicants request respectfully withdrawal of the obviousness rejection of Claims 6 and 23, which additionally relies on Newman et al.

Respectfully submitted,



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